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(71) Applicant *(for all designated States except US)*: UNIVERSITY OF UTAH [US/US]; Technology Transfer Office, Suite #170, 421 Wakara Way, Salt Lake City, UT 84108 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ROBERTS, Jeanette, C. [US/US]; 2377 East Foothill Circle, Salt Lake City, UT 84108 (US). WILMORE, Britta, H. [DE/US]; 3672 South 300 East, Salt Lake City, UT 84115 (US). CASSIDY, Pamela, B. [US/US]; 936 Pennsylvania Place, Salt Lake City, UT 84102 (US). DOMINICK, Pamela, K. [US/US]; 2325 East 2100 South #1, Salt Lake City, UT 84109 (US). SHORT, Megan, D. [US/US]; 53 South Elizabeth Street #2, Salt Lake City, UT 84102 (US).

(74) Agent: SONNTAG, James, L.; P.O. Box 21, Heber City, UT 84032–0021 (US).

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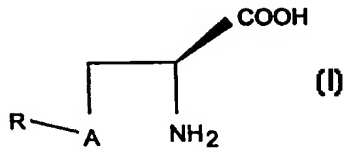
(54) Title: PRODRUGS AND CONJUGATES OF THIOL– AND SELENOL– CONTAINING COMPOUNDS AND METHODS OF USE THEREOF

(57) Abstract

Disclosed is a prodrugs of the formula (I) where A is a sulfur or a selenium, and R is derived from a mono– di– or oligosaccharide. Also disclosed is a prodrug of the formulas (II); where A is sulfur or selenium, R' is derived from a sugar and R' has the formula $(CHOH)_nCH_2OH$, where n is 1 to 5, or R' is an alkyl or aryl group, or R' is =O, and the R'' groups may be the same or different and may be hydrogen, alkyl, alkoxy, carboxy. Also disclosed is a conjugate of an antioxidant vitamin and a thiolamine or selenolamine. Also disclosed is a prodrug of the formula (III); where A is sulfur or selenium, and R' is derived from a sugar and R' has the formula $(CHOH)_nCH_2OH$, where n is 1 to 5, or R' is also an alkyl or aryl group, or R' is =O, and $R^{\ddagger}$ is an alkoxy, or an amine group. Also disclosed is a prodrug of the formula (IV) R is COOH or H, and R' is derived from a sugar and R' has the formula $(CHOH)_nCH_2OH$, where n is 1 to 5, or R' is an alkyl or aryl group, or R' is =O.



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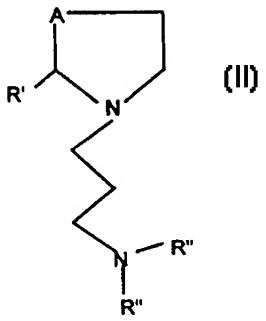

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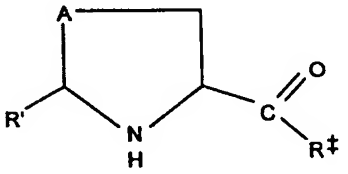

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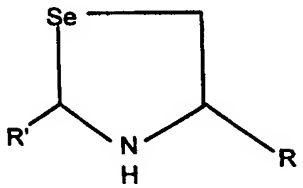

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TITLE

PRODRUGS AND CONJUGATES OF THIOL- AND SELENOL-CONTAINING COMPOUNDS AND METHODS OF USE THEREOF

PRIORITY CLAIM

Priority is hereby claimed to United States Provisional Patent Application 60/055,019, filed August 7, 1997 (which is hereby incorporated by reference).

FIELD OF THE INVENTION

The present invention relates to sulfur- and selenium- containing compounds and methods for using these compounds to protect mammals from toxic insults. More specifically, the present invention relates to prodrugs and conjugates of thiol- or selenol-containing compounds, such as cysteine, cysteamine, glutathione, selenocysteine, selenocysteamine, and the Walter Reed (WR) compounds.

BACKGROUND OF THE INVENTION

Technical Background

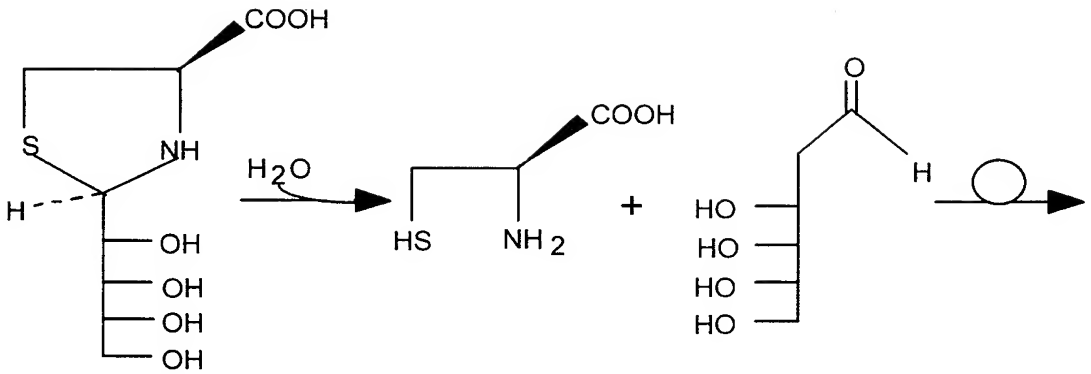
Thiol- or selenol-containing compounds, e.g., cysteine, cysteamine, glutathione, selenocysteine, selenocysteamine, and the WR compounds, are known protective and preventive agents. Potential protective or preventive uses of such agents are widespread, as in reducing the unwanted side effects of chemo- or radiotherapy of cancer, improving cardiovascular function, preventing mutagenesis, preventing the initiation and/or progression of cancer, reducing toxic consequences of planned or unplanned radiation or chemical exposures, slowing the aging process, and preventing cataract formation. New evidence also links these compounds to altered gene expression and enhanced cellular repair processes.

The activity of these thiol- or selenol-containing compounds is mainly due to the sulfur or selenium atom participating in nucleophilic attack on toxic electrophiles, scavenging free radicals, effecting repair of damaged targets through hydrogen atom donation, altering the redox status of the cell, or affecting gene transcription or protein function.

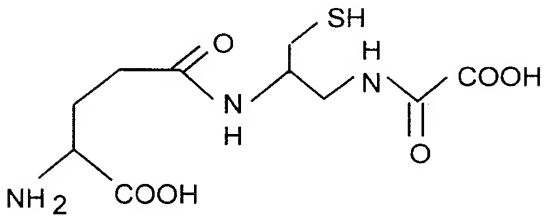
For example, the reduced form of glutathione (Glu-Cys-Gly), a naturally occurring tripeptide with a free sulfhydryl group (SH), serves as a sulfhydryl buffer that maintains the cysteine residues of hemoglobin and other proteins in a reduced state. Glutathione also plays a key role in detoxifying the body by reacting with both endogenous and exogenous compounds, such as hydrogen peroxide and other peroxides.

Evidence suggests that glutathione is useful at protecting the body from the harmful side effects of radiation and chemotherapy that often accompany cancer treatment. Cyclophosphamide (CTX), for example, is a widely used antitumor agent whose clinical utility is limited by its bladder toxicity. During CTX metabolism in the body, a compound, acrolein, is released. Acrolein is thought to be responsible for the urotoxicity of CTX. Glutathione has been implicated in CTX detoxification by conjugating to acrolein.

It has been of significant interest in the art, therefore, to increase glutathione synthesis especially during periods of toxic insults. L- cysteine, a reactant in normal glutathione biosynthesis, is known to increase the synthesis of endogenous glutathione. To date, a significant challenge in the art has been to provide L-cysteine to cells at sufficiently high levels to drive glutathione biosynthesis. As disclosed, for example, in United States Patent 4,868,114 to Nagasawa et al., prodrugs of L-cysteine (i.e., chemical compounds converted to L-cysteine in the cell), such as RibCys, can be used by the cell to drive glutathione biosynthesis shown below.



RibCYS CYSTEINE



GLUTATHIONE

These prodrugs have been shown to offer good protection against a variety of toxic insults. However, the initial prodrugs are highly water soluble and are rapidly excreted by the body.

WR compounds are also of significant interest in the art. Over 4400 WR compounds were prepared and tested at the Walter Reed Army Hospital after World War II in an effort to develop radioprotective compounds that might be employed by military personnel during a nuclear encounter. The single agent with the greatest potential that arose from that extensive effort was WR-2721, which is converted to WR-1065 by enzymatic cleavage. These compounds have several shortcomings, however, including that they possess noteworthy toxicity and little oral activity, greatly reducing their clinical utility.

Finally, selenocysteines are of significant interest in the art for their antioxidant and anticancer properties. In fact, selenium has received significant attention for its ability to inhibit or delay the onset of AIDS caused by HIV infection. Selenium is also a cofactor of glutathione peroxidase, an enzyme which has been implicated in many detoxifying processes.

Selenium is an essential mineral that is critical to the normal functioning of many species, including humans. It also has demonstrated activity as a cancer chemopreventive agent. Selenium-containing compounds appear to have especially high preventive activity against the initiation phase of colorectal cancer, although its chemoprotective ability has been extended to cancers in many organs, caused by a variety of carcinogens.

To achieve this chemopreventive activity, levels of selenium at least five-fold greater than that required for normal nutritional status appear to be necessary. In addition, selenium must be given continuously for maximum inhibition. Unfortunately, selenium is also known for its profound toxicity, making selenium supplementation a distinct challenge.

Current selenium supplements rely on inorganic forms, such as sodium selenite (Na_2SeO_3) or sodium selenate (Na_2SeO_4). While these forms have some value, they are considered more toxic than necessary, and are unlikely to be useful in cancer chemo-prevention. Several organoselenium compounds, which appear to be less toxic in general than the inorganic forms, have been proposed for in vivo use, but the full potential of this strategy has not yet been realized. In general, however, it is very clear that the chemical form in which selenium is introduced consistently shows a marked influence on biological outcomes, including cancer chemoprevention and toxicity.

Selenocysteine is an organic form that is present in the body and is now recognized as the 21st amino acid used in protein synthesis. While it represents a valuable biochemical form, selenocysteine is chemically unstable and difficult to handle, which has undoubtedly deterred its study and use. In addition, even though it possesses greatly reduced inherent toxicity, it still may be too toxic at chemopreventive doses to the therapeutically useful. Accordingly, prodrug forms of selenocysteine that possess reduced inherent toxicity and improved physicochemical properties would be desirable.

Objects of the Invention

It is, therefore, an object of the invention to provide prodrugs and conjugates of thiol- or selenol-containing compounds, such as cysteine, cysteamine, glutathione, selenocysteine, selenocysteamine, and the WR compounds.

Another object of the invention is to provide such thiol- or selenol-containing compounds displaying reduced toxicity and increased clinical utility.

Another object of the invention is to provide such thiol- or selenol-containing compounds with increased lipophilicity that can target a specific organ or region of the body.

Another object of the invention is to provide such thiol- or selenol-containing compounds that can be conjugated to antioxidants, such as vitamin C and E, thus maximizing the effects by providing different agents that work by complementary mechanisms.

Further objects of the invention will become evident in the description below.

BRIEF SUMMARY OF THE INVENTION

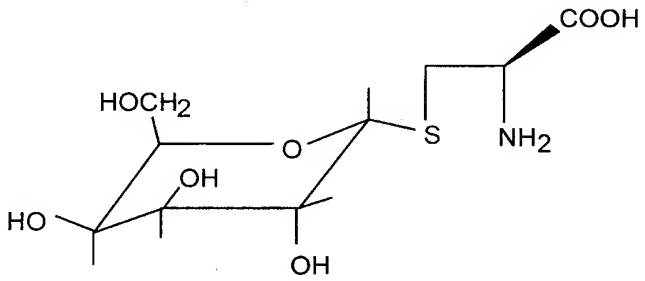
The present invention is directed to novel prodrugs and conjugates of thiol- or selenol-containing compounds, including cysteine, cysteamine, glutathione, selenocysteine, selenocysteamine, and the WR compounds. Potential protective or preventive uses of such agents are widespread, as in reducing the unwanted side effects of chemo- or radiotherapy of cancer, improving cardiovascular function, preventing mutagenesis, preventing the initiation and/or progression of cancer, reducing toxic consequences of planned or unplanned radiation or chemical exposures, slowing the aging process, preventing cataract formation, etc.

Prodrugs are inactive forms of a parent drug that have been created to overcome one or more barriers to their effective use. In the present invention, prodrugs have been designed to overcome the chemical instability and/or possible toxicity barriers that exist with the parent drug.

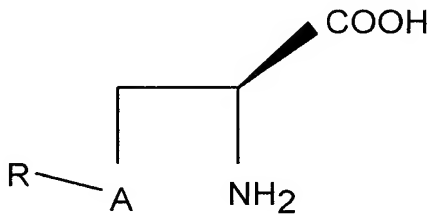
In one embodiment, the invention relates to the design, synthesis, and evaluation of prodrugs of L-cysteine and L-selenocysteine, containing a thioglycoside or selenoglycoside on the free thiol or selenol. The protecting group will, in addition

to protecting the thiol or selenol from oxidation, permit the targeting of specific sites within the body.

For example, the galactose protected cysteine shown below will target the liver and will enter the cytoplasm of hepatocytes. Delivering L-cysteine to hepatocytes has numerous uses, including protection against hepatotoxins, such as acetaminophen, and against side effects caused by local radiation treatments.



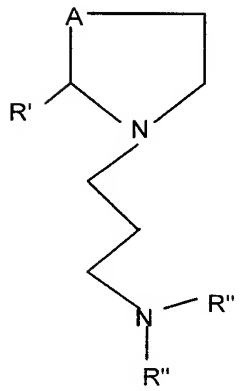
The cysteine/selenocysteine prodrugs can be depicted by the formula:



where A is a sulfur or a selenium, and R is derived from a mono- di- or oligo-saccharide, such as ribose, galactoxe, glucose, or mannose.

A second embodiment relates to the design, synthesis, and evaluation of novel prodrugs that are derivatives of cysteamines or selenocysteamines, such as of WR compounds, particularly WR-1065. The prodrug strategy is similar to that employed for L-cysteine, using a protecting group R'. R is typically a sugar, such as ribose. The modified WR prodrugs have numerous uses including protection against the side effects of radiation and chemotherapy, radiation and chemical induced mutations, such as from exposure to radiation during a nuclear accident or chemical spill, and even spontaneous mutations which are the cause of most cancers.

These prodrugs can be described by the formulas;

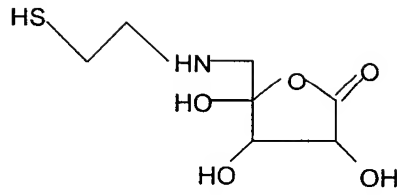


where A is sulfur or selenium, R' is derived from a sugar and has the formula $(CHOH)_nCH_2OH$, where n is 1 to 5. R' may also be hydrogen, an alkyl or aryl group, such as methyl, ethyl, benzyl, carboxyl, polyhydroxyalkyl, or phenyl, or may also be =O. The R" groups may be the same or different and may be alkyl, alkoxy, carboxy, such as acetyl, methyl or ethyl.

These novel thio- and selenol-containing compounds overcome several problems facing the art, including toxicity, water-solubility, and lack of target specificity. First, the protective or preventive activity and clinical utility will be greatly enhanced by converting the cysteine, cysteamine, glutathione, selenocysteine, selenocysteamine, and WR compounds, to thiazolidine and selenazolidone prodrug forms. These prodrugs provide a slow release form of the thiol-/selenol-amine, which greatly reduces observed toxicity (with related compounds), but provides the active agent after enzymatic or non-enzymatic biotransformation

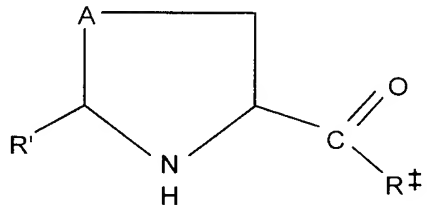
In a third embodiment, the invention relates to the design, synthesis, and evaluation of novel covalent conjugates of thiolamines or selenolamines and antioxidant vitamins, e.g., Vitamin E and Vitamin C. These compounds include conjugates of any of the prodrug compounds of the invention defined above conjugated with Vitamin C or Vitamin E. Also contemplated by the invention are conjugates of antioxidant vitamins with the following thiol- and selenol-amines and derivatives thereof; cysteine, cystine, cysteamine, cystamine, glutathione, selenocysteine, selenocysteamine, selenocystine, selenocystamine, and WR compounds (WR-1065 and WR-33278).

An example, shown below is a conjugate of cysteamine and Vitamin C.



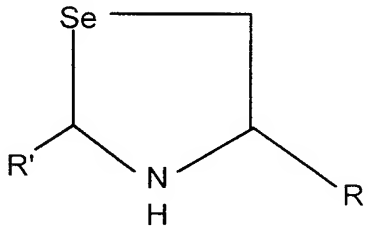
These compounds are effective because protective or preventive treatment of toxic insult will be far more effective if thiol- or selenol-containing compounds are delivered together with antioxidants such as vitamin C and E which also play a protective and preventative action in the body. The complementary mechanisms of these compounds would increase the overall effectiveness of treatment.

In yet another embodiment, the invention relates to the design, synthesis, and evaluation of novel L-cysteine prodrugs which have been modified with ester or amine groups at the carboxylic acid position. These can be described by formula;



where A is sulfur or selenium, and R' is derived from a sugar and has the formula $(CHOH)_nCH_2OH$, where n is 1 to 5. R' may also be an alkyl or aryl group, such as methyl, ethyl, benzyl, carboxyl, or phenyl, or may also be =O. $R^{\ddagger}$ is an alkoxy, such as $-OR^1$ where R^1 is ethyl, methyl. $R^{\ddagger}$ may also be an amine group ($-NR^{\dagger}_2$) where the $R^{\dagger}$ groups are the same or different and hydrogen or an alkyl group, such as methyl.

Yet another embodiment of the invention is the condensation product of a selenolamine and a carbonyl donor characterized by the formula:



where R is COOH (prodrug of L-selenocysteine) or is H (prodrug of selenocysteamine). R' is derived from a sugar and has the structure $(CHOH)_nCH_2OH$.

and where n is 1 to 5; an alkyl or aryl group, such as methyl, ethyl, benzyl, phenyl or carboxyl; or =O.

DETAILED DESCRIPTION OF THE INVENTION

I. Thioglycoside Prodrugs

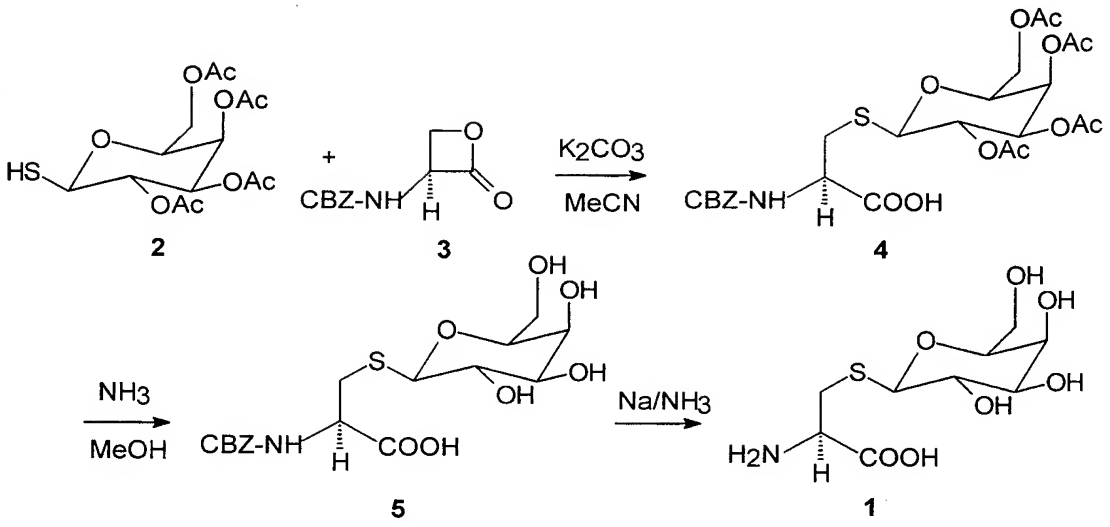
1. Agent Design

Prodrugs of L-cysteine and L-selenocysteine containing a thioglycoside or selenoglycoside on the free thiol or selenol can be prepared. The protecting group will, in addition to protecting the thiol or selenol from oxidation, permit the targeting of specific sites within the body.

For example, a galactose protected cysteine will target the liver and will enter the cytoplasm of hepatocytes. Delivering L-cysteine to hepatocytes has numerous uses, including protection against hepatotoxins, such as acetaminophen, and against side effects caused by local radiation treatments.

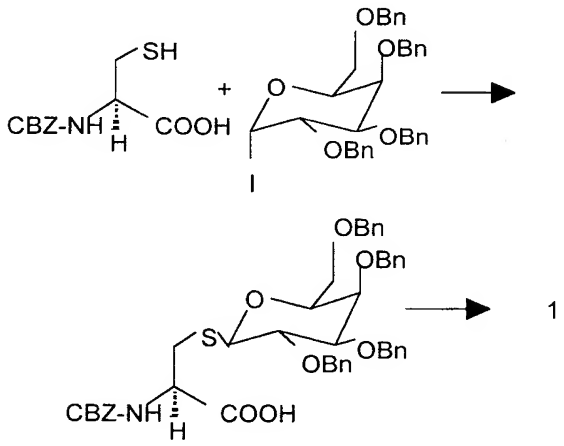
2. Chemical Synthesis.

The prodrug of L-cysteine (compound 1) was prepared as shown in Scheme 1. The protected thiogalactose analog 2 was alkylated with L-serine β-lactone 3 in the presence of potassium carbonate. The protected thiopyranoside 4 was isolated in 70% yield after purification by silica gel chromatography. The acetate protecting groups were removed by treatment of 4 with methanolic ammonia, giving 5. Sodium in liquid ammonia was then used to remove the amino protecting groups, giving the target prodrug 1.



Scheme I

An alternative route to prodrug 1 features the formation of the thiopyranoside bond by displacement of iodine from a suitably protected galactosyl iodide (Scheme II). This route would eliminate the need to prepare β-lactone 3 (the purification of which is difficult and not very versatile with respect to the range of α-amino protecting groups that can be used) and makes it possible to use hydroxyl (on the sugar) and amino (on the cysteine) protecting groups that can be removed in a single reaction to generate the target compound 1.



Scheme II

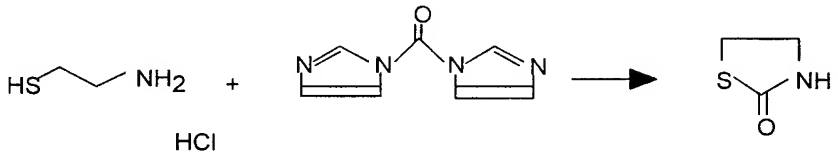
II. Thiazolidine Prodrugs of Walter Reed (WR) Compounds

1. Agent Design

Thiazolidine prodrug forms can be prepared from the thiolamine and virtually any carbonyl-containing compound, particularly the sugars, such as aldose monosaccharide, D-ribose, as an aldehyde that results in thiazolidines with superior protective activity. Numerous sugars or alkyl/aryl aldehydes or ketones can be used. These product thiazolidines will undergo non-enzymatic dissociation to liberate the active thiolamine. In addition, the 2-oxo derivatives, can be prepared, which require enzymatic action to liberate the active thiolamine.

2. Chemical Synthesis

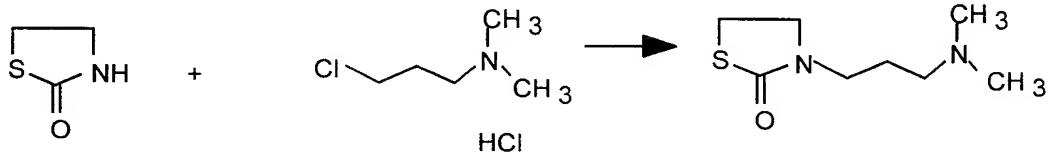
a. 2-Thiazolidinone (prodrug of cysteamine and starting material for other syntheses) Carbonyl diimidazole (15.75 g 0.097 mol) was dissolved, with heating, in 150 ml acetonitrile, which has been degassed and flushed with nitrogen. To this was added, cysteamine hydrochloride (10.01 g, 0.088 mol), potassium carbonate (13.50 g, 0.098 mol), and 18-crown-6 (catalytic amount), and the solution was stirred at reflux (~80°C) for 19 hours. After this time, solvent was removed in vacuo. The crude product was redissolved in 100 ml 5% sodium carbonate and refluxed for 1 hour, then acidified to pH 2 with concentrated hydrochloric acid. The resulting solid was removed via filtration and the product was extracted from the filtrate into ethyl acetate (12 x 35 ml). The combined organic portion was washed with 1 M potassium chloride and saturated sodium chloride (50 ml each), dried over sodium sulfate, filtered, and dried in vacuo. Yield was 84 g, 42%.



b. (N',N'-Dimethyl-3-aminopropyl)-2-thiazolidinone

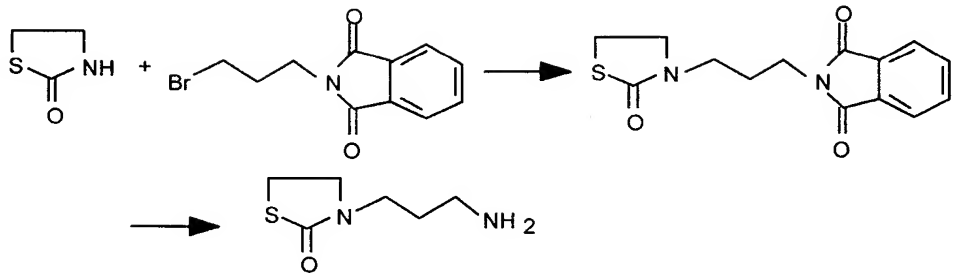
To a solution of 2-thiazolidinone (4.15 g, 40.18 mmol) in acetonitrile (60 ml) were added potassium carbonate (13.3 g 96.2 mmol), N,N-dimethyl-3-aminopropyl chloride hydrochloride (7.63 g, 48.3 mmol), and 18-crown-6 (catalytic amount). The

mixture was refluxed for 18 hours, solvent removed in vacuo, then redissolved in dichloromethane and 1 M potassium chloride (40 ml each). The aqueous phase was isolated and extracted twice with 30 ml portions of dichloromethane. The combined organic fraction was washed with saturated sodium chloride (~50 ml), dried over sodium sulfate, filtered, and dried in vacuo. The crude product was purified via silica gel chromatography, using a 10:1 ratio of silica gel A, 200-425 mesh, and eluting with 5% methanol in chloroform, yielding 1.15 g (15%) pure product.



c. 3-(3 -Aminopropyl)-2-thiazolidinone

To a solution of 2-thiazolidinone (0.994 g, 9.64 mmol) in acetonitrile (10 ml) were added N-phthalimido-3-bromopropylamine (2.88 g, 10.7 mmol), potassium carbonate (1.64 g, 11.9 mmol), and 18-crown-6 (catalytic amount). The mixture was refluxed about 17 hours, solvent was removed in vacuo, and the resulting solid was redissolved in 1 M potassium chloride and dichioromethane (~25 ml each). The aqueous phase was separated and extracted with 2 x 25 ml dichloromethane. The combined organic fraction was dried over sodium sulfate, filtered, and dried in vacuo. The crude product was recrystallized from acetone/methanol to give 1.54 g (55% yield). To a warmed solution of the phthalimido protected amine (1.53 g, 5.27 mmol) in 6:1 isopropanol:water was added sodium borohydride (1.01 g, 26.7 mmol), and the mixture was stirred at 60°C for 22 hours. Glacial acetic acid (5.4 ml) was added, and the solution was stirred at 80°C for 2 hours, then the solution was cooled and dried in vacuo. The product was redissolved in 6 N hydrochloric acid, washed with ether (2 x 30 ml), then dried in vacuo. The product was purified via recrystallization from hot water.



Similar procedures are employed to produce the terminal monomethylated form, as well as the terminal N-acetyl compound. In addition, various ally! or aryl aldehydes or ketones are employed to produce the corresponding allyl or aryl substituent at the 2 position, as opposed to the 2-oxo derivatives presented above.

Radioprotection in E. coli AB1157

A well characterized bacterial system was used as an initial screen for radioprotective activity of the novel compounds. A single colony of the bacteria, growing on a plate of LB medium (10 g tryptone, 5 g yeast extract, plus 5 g NaCl in 1 L water), was inoculated into 2 mL LB and incubated overnight. 20 mL LB medium were then inoculated with 600 μL of the overnight culture, and incubated with shaking at 37°C, 250 rpm. The cells were collected and washed with phosphate buffered saline. At this point the bacteria could be irradiated, treated with drug, etc., as outlined below. After dilution of the treated cells to 100 cells per 100 μL, they are plated out and incubated overnight. Cell viability is then measured by colony forming ability.

Growth curves were generated for the bacteria in the absence of any treatment to provide experience with basic handling as well as important baseline information. The radiation dose response of the system was investigated irradiating bacterial cultures in a Shepherd Mark I ^{137}Cs irradiator over a dose range of 0 to 1 kGy. The dose-response curves are linear and reproducible from day to day. From these data, a radiation dose of 0.6 kGy was chosen for the initial radioprotection experiments in order to achieve approximately a 0.1% survival in the unprotected cultures, a common target for these types of studies.

The toxicity of the compounds of interest in this system was explored. Administering the 2-oxocysteamine prodrug completely eliminated the profound toxicity observed with cysteamine itself; neither WR-1065 nor its 2-oxo prodrug produced any toxicity in this assay.

Radioprotection experiments were also conducted in the bacterial system. For these experiments, the bacteria were grown to log phase and then treated with the agent of choice (parent, prodrug, or positive control) for 1 hour before irradiation at 0.6 kGy. Surviving fraction compared to that seen in control (untreated) cells, which were not irradiated, was then calculated. The positive control homocysteine thiolactone (HCTL) and WR-1065 showed the greatest amount of protection.

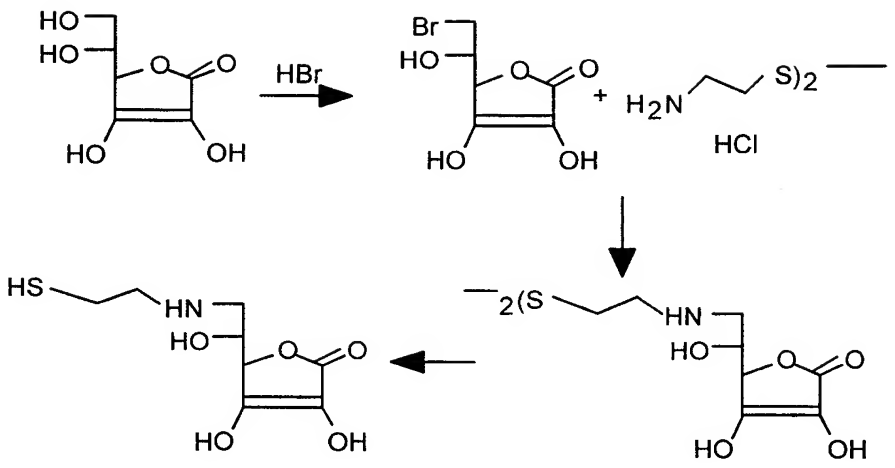
III. Covalent Conjugates of Thiol- or Selenol-amines and Antioxidant Vitamins

1. Agent Design

The present invention focuses on the antioxidant vitamins C and E, and the thiol or selenol agents, cyst(e)ine, cyst(e)amine, N-acetylcysteine, glutathione, WR-1065/WR-33278, selenocysteine, and selenocysteamine.. This represents a minimum of 24 combinations of the two classes. It will be appreciated by those skilled in the art that other antioxidants can be conjugated to these thiol- or selenol-containing compounds.

2. Chemical Synthesis

The schemes below summarize potential approaches using cysteamine for illustrative purposes. Many permutations are available.



IV. Modified Prodrugs of L-Cysteine of L-Selenochysteine

1. Agent Design

These prodrugs possess a modified carboxyl group compared to unmodified prodrugs of L-cysteine and L-selenocysteine. The purpose of the modification is to reduce the hydrophilicity of the prodrugs and improve their cellular uptake and retention in the body. The modifications include converting the carboxyl group to an ester or amide functionality.

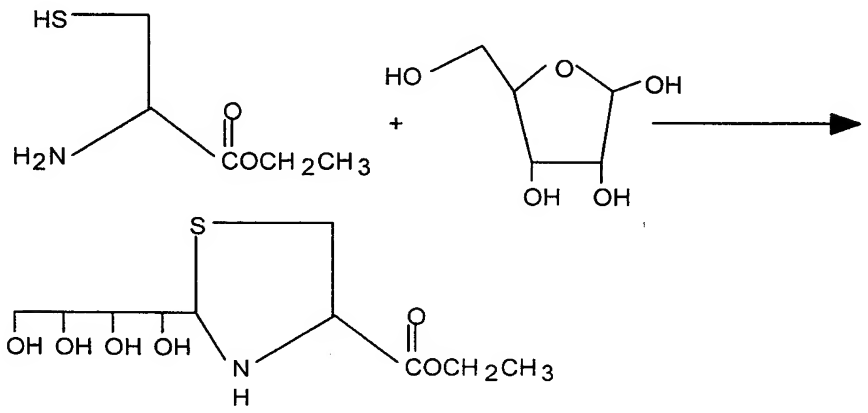
2. Chemical Synthesis

Ester prodrugs were prepared beginning with commercially available L-cysteine methyl or ethyl ester. The ester is combined with an equimolar amount of carbonyl donor, i.e., acetaldehyde, the aldose monosaccharide, D-ribose, or phenyl chloroformate. The amide prodrugs were prepared by the initial synthesis of L-cysteine amides (not commercially available) from L-cysteine and the appropriate amine, such as ammonia, methylamine, or dimethylamine. The synthesized L-cysteine amides were then reacted with an equimolar amount of carbonyl donor, i.e., acetaldehyde, the aldose monosaccharide, D-ribose, or phenyl chloroformate.

Modified prodrugs of L-selenocysteine can be constructed in an identical fashion. However, L-selenocysteine methyl or ethyl ester are prepared by the

esterification of L-selenocysteine with methanol or ethanol because these compounds are not commercially available.

For example, the reaction of L-cysteine ethyl ester and D-ribose may be as follows;



V. Selenazolidines: Modified Prodrugs of Selenocysteine and Selenocysteamine

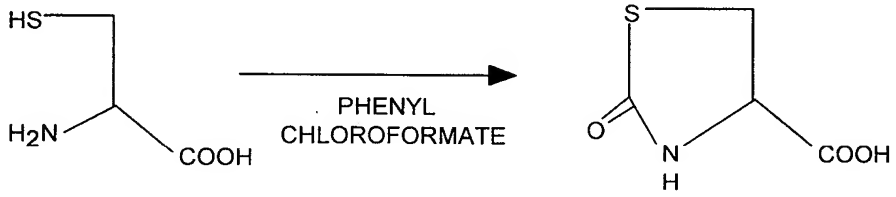
1. Agent Design

Current selenium supplements rely on inorganic forms. While these forms have some value, they are considered more toxic than necessary, and are unlikely to be useful in cancer chemoprevention or in AIDS supplementation. Several organoselenium compounds, which appear to be less toxic in general than the inorganic forms, have been proposed for in vivo use, but the full potential of this strategy has not yet been realized. In general, however, it is very clear that the chemical form in which selenium is introduced consistently shows a marked influence on biological outcomes. Selenocysteine is an organic form that is present in the body and is now recognized as the 21st amino acid used in protein synthesis. Due to its differential metabolism, it represents the biochemically superior form in which to supply the body with selenium. Unfortunately, selenocysteine is chemically unstable and difficult to handle. Therefore, prodrug forms of the amino acid have been designed which represent chemically superior forms. Similar arguments hold for selenocysteamine as well.

2. Chemical Synthesis

Selenocysteine/selenocysteamine prodrugs can be synthesized by the chemical condensation of the selenolamine with a carbonyl donor. Alkyl or alkyl aldehydes or ketones can be used, including simply donors such as acetaldehyde or benzaldehyde, or aldose or ketose mono- or di-saccharides. In addition, carbonyl donors such as phenyl chloroformate can be used to produce 2-oxo derivatives.

For example, the reaction of L-selenocysteine and phenyl chloroformate is illustrated.

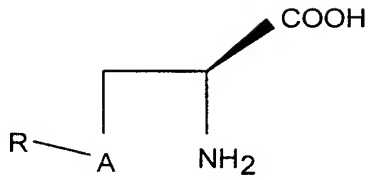


While this invention has been described with reference to certain specific embodiments and examples, it will be recognized by those skilled in the art that many variations are possible without departing from the scope and spirit of this invention, and that the invention, as described by the claims, is intended to cover all changes and modifications of the invention which do not depart from the spirit of the invention.

CLAIMS

What is claimed is:

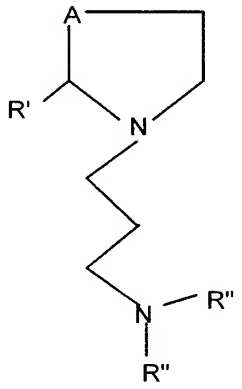
1. A prodrug of the formula:



where A is a sulfur or a selenium, and R is derived from a mono- di- or oligo-saccharide.

2. A prodrug of Claim 1 wherein R is derived from ribose, galactose, glucose, or mannose.

3. A prodrug of the formula;



where A is sulfur or selenium,

R' is derived from a sugar and R' has the formula $(CHOH)_nCH_2OH$, where n is 1 to 5, or

R' is an alkyl or aryl group, or

R' is =O, and

the R" groups may be the same or different and may be hydrogen, alkyl, alkoxy, or carboxy.

4. A prodrug of Claim 3 wherein R' is methyl, ethyl, benzyl, carboxyl, phenyl, polyhydroxyalkyl.

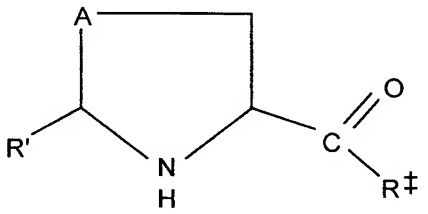
5. A prodrug of Claim 3 wherein R" is hydrogen, acetyl, methyl or ethyl.

6. A conjugate of an antioxidant vitamin and a thiolamine or selenolamine.

7. A conjugate as in Claim 6 wherein the antioxidant vitamin is Vitamin C or Vitamin E.

8. A conjugate as in Claim 6 wherein the thiolamine or selenolamine selected from or a derivative of the group comprising cysteine, cystine, cysteamine, cystamine, glutathione, selenocysteine, selenocysteamine, selenocystine, selenocystamine, WR-1065, and WR-33278.

9. A prodrug of the formula;



where A is sulfur or selenium, and

R' is derived from a sugar and R' has the formula $(CHOH)_nCH_2OH$, where n is 1 to 5, or

R' is also be an alkyl or aryl group, or

R' is =O, and

$R^‡$ is an alkoxy, or an amine group.

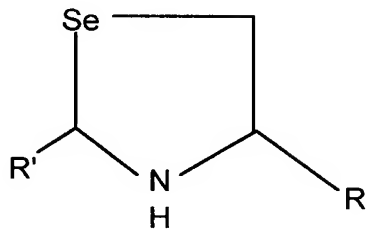
10. .A prodrug as in Claim 9 wherein $R^‡$ is $-OR^1$ where R^1 is ethyl, or methyl.

11. A prodrug as in Claim 9 wherein R' is methyl, ethyl, benzyl, carboxyl, or phenyl.

12. A prodrug as in Claim 9 wherein $R^‡$ is $-NR^†_2$, wherein the $R^†$ groups are the same or different and are hydrogen or alkyl.

13. A prodrug as in Claim 12 wherein at least one $R^{\dagger}$ is methyl.

14. A prodrug of the formula:



R is COOH or H, and

R' is derived from a sugar and R' has the formula $(CHOH)_nCH_2OH$, where n is 1 to 5, or

R' is an alkyl or aryl group, or

R' is =O.

15. A prodrug of Claim 14 wherein R' is methyl, ethyl, benzyl, carboxyl, or phenyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/16324

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07H 5/04, 5/06, 15/00, 17/00
US CL :536/17.9, 18.7

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/17.9, 18.7

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, 4,868,114 A (NAGASAWA et al) 19 September 1989, column 2, lines 53-68.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 01 DECEMBER 1998	Date of mailing of the international search report 29 DEC 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ELLI PESELEV Telephone No. (703) 308-1235

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